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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/084,380

02/28/2002

Daniel G. Chain

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3496

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7590

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EXAMINER

EMCH, GREGORY S

ART UNIT

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/084,380	<b>Applicant(s)</b> CHAIN, DANIEL G.	
	<b>Examiner</b> Gregory S. Emch	<b>Art Unit</b> 1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 19 February 2009.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 14, 19, 20, 25, 55, 56, 72, 75 and 93-120 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 14, 19, 20, 25, 55, 56, 72, 75 and 93-120 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>01/27/09; 05/12/09</u> .                                      | 6) <input type="checkbox"/> Other: _____                          |

### **DETAILED ACTION**

The finality of the last Office action is withdrawn, and new grounds of rejection are set forth below.

#### ***Formal Matters***

Claims 14, 19, 20, 25, 55, 56, 72, 75 and 93-120 are pending in the instant application.

Upon further consideration the election of species requirement set forth in the office action dated 19 August 2008 is hereby withdrawn as the examination of two species is not an exhaustive burden. Claims 99-104 and 109-120 are hereby rejoined for examination of the merits.

Claims 14, 19, 20, 25, 55, 56, 72, 75 and 93-120 are under examination in the instant office action.

#### ***Information Disclosure Statement***

The information disclosure statements (IDS) submitted on 27 January 2009 and 12 May 2009 were filed after the mailing date of the final Office action on 26 November 2008. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements are being considered by the examiner.

#### ***Response to Arguments***

Applicant's arguments, see pp.2-6 of the pre-appeal brief request for review, filed 19 February 2009, with respect to the rejection(s) of claim(s) 14, 19, 20, 25, 55, 56, 72, 75, 93-98 and 105-108 under 35 U.S.C. 112, second paragraph have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made as set forth below.

### ***Duplicate Claims Warning***

Applicant is advised that should claims 113-116 be found allowable, claims 117-120 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 14, 19, 20, 25, 55, 56, 93-98 and 105-108 are rejected under 35 U.S.C. 103(a) as being unpatentable over Becker et al. (EP 0 613 007, published 31 August 1994) and further in view of US 5,965,614 to Audia et al. (issued 12 October 1999; effective priority date of 22 November 1996).

EP 0 613 007 (Becker) teaches the use of conformationally-specific antibodies and antibody fragments which bind to amyloid  $\beta$  (A $\beta$ ) peptides for the treatment of amyloid accumulation diseases, such as Alzheimer's disease. Some of these antibodies bind selectively with those A $\beta$  peptides, which are predominantly in a  $\beta$ -sheet conformation and some of the antibodies bind to A $\beta$  peptides, which have adopted a random coil or  $\alpha$ -helix conformation (col.5, lines 42-50; col.7, lines 49-52). Becker teaches that such antibodies would be useful in inhibiting the neurotoxicity associated with the accumulation of oligomeric A $\beta$  in Alzheimer's disease (col.1, lines 1-18; col.5, lines 27-41). Becker teaches antibodies that bind to dissociated (i.e., soluble A $\beta$ , including A $\beta$  1-40) and those that bind to aggregated A $\beta$ , wherein administration of both types of antibodies is therapeutically effective in treating the neurotoxicity associated with Alzheimer's disease (col.2, lines 38-50; col.5, lines 42-50; col.7, lines 49-52), as in

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claims 14 and 20. Becker teaches monoclonal antibodies, humanized antibodies, chimeric antibodies, antibody binding fragments (including Fab, F(ab')<sub>2</sub> and Fv fragments) and single-chain antibodies (col.5, line 50 – col.6, line 12), as in claims 19, 25, 55, 56, 93-98 and 105-108. It is noted that the active method steps of independent claims 14, 20 and 105 are essentially the same, i.e. said claims require contacting an A $\beta$  peptide with an exogenous free-end specific antibody in the cerebrospinal fluid (CSF) of an Alzheimer's patient. The contacting step in these claims are taught by Becker, since Becker teaches administration of the antibodies for therapeutic treatment of Alzheimer's disease patients, which would necessarily reach the cerebrospinal fluid of the patients (see e.g. col.8, lines 16-42). That is, the active step recited in the claims is administering (in general) and does not require administration to the CSF. The claims are construed to encompass any route of administration, and since Becker teaches that the method is sufficient to treat Alzheimer's, the antibodies must reach the CSF. It is noted that the instant specification (see paragraphs [0010], [0043], and [0090]) indicates that the methods can include routes of administration other than directly to the CSF. Since the antibodies would necessarily reach the CSF and bind the A $\beta$  peptide therein, Becker inherently teaches a method of obtaining an amyloid  $\beta$ -peptide-antibody complex which comprises forming a composition consisting essentially of: an A $\beta$  antibody, cerebrospinal fluid and said A $\beta$  peptide, as in claims 93-98.

Becker does not explicitly teach contacting *in vivo* soluble A $\beta$  in the cerebrospinal fluid of an Alzheimer's patient with an exogenous free-end specific antibody which is targeted to a free N-terminus or a free C-terminus of A $\beta$  1-40. However, Audia teaches

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that the A $\beta$  monoclonal antibody 3D6 binds specifically to residues 1-5 of A $\beta$  and that said antibody does not recognize secreted amyloid precursor protein (APP) or full-length APP, but detects A $\beta$  species with an amino terminal aspartic acid, i.e. at position 1 of A $\beta$  peptide (col.49, lines 21-24), as in claims 55, 56, 93-98 and 105-108. Audia's antibody is "free-end specific" as instantly claimed, since it does not bind to APP (see description at e.g. p.8, lines 10-17 of the specification). Audia does not teach administration of the free end specific antibody for inhibiting accumulation and neurotoxicity associated with Alzheimer's disease.

However, it would have been *prima facie* obvious to the artisan of ordinary skill in the art at the time the invention was made to arrive at the claimed invention by combining the disclosures of Becker and Audia. The skilled artisan would have been motivated to use the 3D6 antibody, i.e. which is a free-end specific antibody directed to the N-terminus of A $\beta$ , in Becker's therapeutic methods because Audia teaches that said antibody is highly specific for A $\beta$  and does not cross react with other closely related molecules, such as APP. That is, since Becker teaches that administration of any A $\beta$  antibody would be useful to treat Alzheimer's disease and Audia teaches that the 3D6 antibody specifically targets the art-recognized peptide involved in the neuropathology of said disease, it would be obvious to use Audia's antibody in Becker's therapeutic methods. Thus, the skilled artisan would have had a reasonable expectation of success that the 3D6 antibody would be successful in treating the neurotoxicity associated with Alzheimer's disease, since it specifically targets A $\beta$ , which is associated with the neurotoxicity in Alzheimer's disease.

Claims 14, 19, 20, 25, 55, 56, 93-98 and 105-108 are rejected under 35 U.S.C. 103(a) as being unpatentable over Becker et al. (EP 0 613 007, published 31 August 1994), further in view of US 5,965,614 to Audia et al. (issued 12 October 1999; effective priority date of 22 November 1996) and as evidenced by Johnson-Wood et al. (PNAS, Feb. 1997, citation AO on IDS dated 03 June 2002).

It is noted that the instant rejection is virtually identical to the rejection set forth above but with further motivation provided by the prior art. EP 0 613 007 (Becker) teaches as set forth above but does not explicitly teach contacting *in vivo* soluble A $\beta$  in the cerebrospinal fluid of an Alzheimer's patient with an exogenous free-end specific antibody which is targeted to a free N-terminus or a free C-terminus of A $\beta$  1-40. However, Audia teaches that the A $\beta$  monoclonal antibody 3D6 binds specifically to residues 1-5 of A $\beta$  and that said antibody does not recognize secreted amyloid precursor protein (APP) or full-length APP, but detects A $\beta$  species with an amino terminal aspartic acid, i.e. at position 1 of A $\beta$  peptide (col.49, lines 21-24), as in claims 55, 56, 93-98 and 105-108. Audia's antibody is "free-end specific" as instantly claimed, since it does not bind to APP (see description at e.g. p.8, lines 10-17 of the specification). Audia does not teach administration of the free end specific antibody for inhibiting accumulation and neurotoxicity associated with Alzheimer's disease.

However, it would have been *prima facie* obvious to the artisan of ordinary skill in the art at the time the invention was made to arrive at the claimed invention by combining the disclosures of Becker and Audia. The skilled artisan would have been

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motivated to use the 3D6 antibody, i.e. which is a free-end specific antibody directed to the N-terminus of A $\beta$ , in Becker's therapeutic methods because Audia teaches that said antibody is highly specific for A $\beta$  and does not cross react with other closely related molecules, such as APP. That is, since Becker teaches that administration of any A $\beta$  antibody would be useful to treat Alzheimer's disease and Audia teaches that said antibody specifically targets the art-recognized peptide involved in the neuropathology of said disease, it would be obvious to use Audia's antibody in Becker's therapeutic methods. Furthermore, Johnson-Wood teaches that 3D6 is free-end specific (p. 1551, first column, section on Abeta measurement), and that it binds to amyloid plaques very well (see Figure 4 and p. 1553, paragraph spanning the 2 columns). This guides the artisan of ordinary skill to select 3D6 based on its superior ability to bind the plaques known to be associated with Alzheimer's disease. Thus, the skilled artisan would have had a reasonable expectation of success that the 3D6 antibody would be successful in treating the neurotoxicity associated with Alzheimer's disease, since it specifically targets A $\beta$  and binds to A $\beta$  plaques, which are associated with the neurotoxicity in Alzheimer's disease.

Claims 14, 19, 20, 25, 72, 75, 99-104 and 109-120 are rejected under 35 U.S.C. 103(a) as being unpatentable over Becker et al. (EP 0 613 007, published 31 August 1994) and further in view of Mak et al. (Polyclonals to beta-amyloid(1-42) identify most plaque and vascular deposits in Alzheimer cortex, but not striatum. Brain Res. 1994 Dec 19;667(1):138-42).

As set forth above, Becker teaches the use of conformationally-specific antibodies and antibody fragments which bind to amyloid  $\beta$  ( $A\beta$ ) peptides for the treatment of amyloid accumulation diseases, such as Alzheimer's disease. Some of these antibodies bind selectively with those  $A\beta$  peptides, which are predominantly in a  $\beta$ -sheet conformation and some of the antibodies bind to  $A\beta$  peptides, which have adopted a random coil or  $\alpha$ -helix conformation (col.5, lines 42-50; col.7, lines 49-52). Becker teaches that such antibodies would be useful in inhibiting the neurotoxicity associated with the accumulation of oligomeric  $A\beta$  in Alzheimer's disease (col.1, lines 1-18; col.5, lines 27-41). Becker teaches antibodies that bind to dissociated, (i.e., soluble  $A\beta$ , including  $A\beta$  1-40) and those that bind to aggregated  $A\beta$ , wherein administration of both types of antibodies is therapeutically effective in treating the neurotoxicity associated with Alzheimer's disease (col.2, lines 38-50; col.5, lines 42-50; col.7, lines 49-52), as in claims 14 and 20. Becker teaches monoclonal antibodies, humanized antibodies, chimeric antibodies, antibody binding fragments (including Fab,  $F(ab')_2$  and Fv fragments) and single-chain antibodies (col.5, line 50 – col.6, line 12), as in claims 19, 25, 99-104 and 109-120. It is noted that the active method steps of independent claims 14, 20, 109, 113 and 117 are essentially the same, i.e. said claims require contacting an  $A\beta$  peptide with an exogenous free-end specific antibody in the cerebrospinal fluid of an Alzheimer's patient. The contacting step in these claims are taught by Becker, since Becker teaches administration of the antibodies for therapeutic treatment of Alzheimer's disease patients, which would necessarily reach the cerebrospinal fluid of the patients (see e.g. col.8, lines 16-42). That is, the active step

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recited in the claims is administering (in general) and does not require administration to the CSF. The claims are construed to encompass any route of administration, and since Becker teaches that the method is sufficient to treat Alzheimer's, the antibodies must reach the CSF. It is noted that the instant specification (see paragraphs [0010], [0043], and [0090]) indicates that the methods can include routes of administration other than directly to the CSF. Since the antibodies would necessarily reach the CSF and bind the A $\beta$  peptide therein, Becker inherently teaches a method of obtaining an amyloid  $\beta$ -peptide-antibody complex which comprises forming a composition consisting essentially of: an A $\beta$  antibody, cerebrospinal fluid and said A $\beta$  peptide, as in claims 99-104.

Becker does not explicitly teach contacting *in vivo* soluble A $\beta$  in the cerebrospinal fluid of an Alzheimer's patient with an exogenous free-end specific antibody which is targeted to a free C-terminus of A $\beta$  1-40, as in claims 72, 75, 99-104 and 109-120. However, Mak teaches that polyclonal antibodies to A $\beta$  34-40 bind to A $\beta$  1-40 but not do not bind to A $\beta$  1-42 (see p.138, abstract and second paragraph). Since the antibodies do not bind to a longer form of A $\beta$  (A $\beta$  1-42), the antibodies would not bind to APP either since APP contains A $\beta$  1-42. It is noted that Mak teaches that the antibody "was predominantly reactive against  $\beta$ 40 and was specific for  $\beta$ 40 after absorption on  $\beta$ 42" (p. 138, 2<sup>nd</sup> paragraph). It would be obvious to the artisan to perform the same method steps for purification of the antibody and use said antibody after it has been purified (as in the cited portion of Mak's disclosure). This would result in an antibody that is more specifically targeted to the A $\beta$  1-40 peptide, which Mak teaches is involved in disease

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pathology. Mak does not teach administration of the free end specific antibody for inhibiting accumulation and neurotoxicity associated with Alzheimer's disease.

However, it would have been *prima facie* obvious to the artisan of ordinary skill in the art at the time the invention was made to arrive at the claimed invention by combining the disclosures of Becker and Mak. The skilled artisan would have been motivated to use the antibodies to A $\beta$  34-40, i.e. which is a free end-specific antibody directed to the C-terminus of A $\beta$  1-40, in Becker's therapeutic methods. This is because Mak teaches that said antibodies are highly specific for A $\beta$  1-40, that this peptide is involved in the neuropathology of Alzheimer's disease, and that this peptide is the major species present in the CSF of Alzheimer's disease patients (see p.138, first paragraph). Moreover, given that Becker teaches monoclonal antibodies and other chimeric antibodies, it would be obvious for the artisan of ordinary skill to generate a monoclonal antibody from Mak's polyclonals. Thus, the artisan would have had a reasonable expectation of success that the antibodies to A $\beta$  34-40 would be successful in treating the neurotoxicity associated with Alzheimer's disease.

### ***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregory S. Emch whose telephone number is (571) 272-8149. The examiner can normally be reached 9:00 am - 5:30 pm EST (M-F).

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey J. Stucker can be reached at (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/G.E./

Gregory S. Emch  
Patent Examiner  
Art Unit 1649  
21 May 2009

/Daniel E. Kolker/  
Primary Examiner, Art Unit 1649  
May 22, 2009